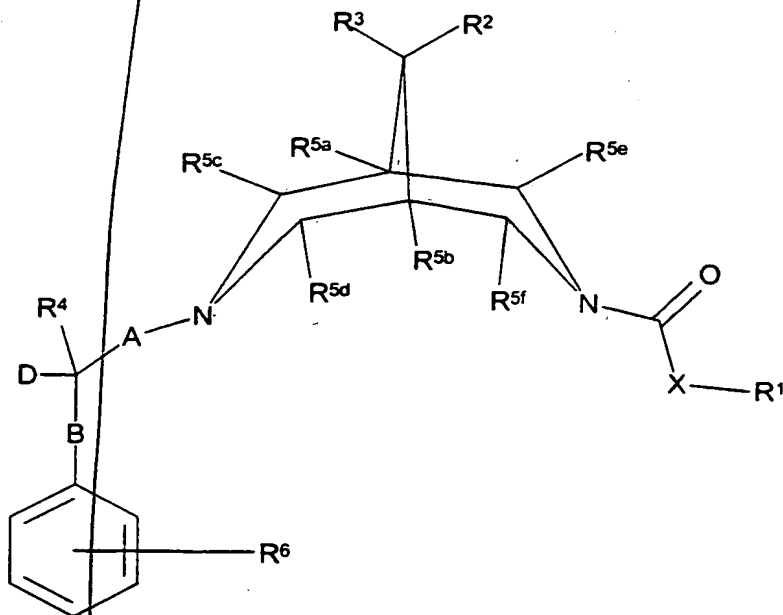


AMENDED CLAIMS

[received by the International Bureau on 18 December 2000 (18.12.00);
original claim 1 amended; remaining claims unchanged (4 pages)]

1. A compound of formula I,



wherein

R^1 represents C_{1-12} alkyl, $-(CH_2)_a$ -aryl, or $-(CH_2)_a$ -Het¹ (all of which are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, halo, cyano, nitro, C_{1-4} alkyl and/or C_{1-4} alkoxy);

a represents 0, 1, 2, 3, or 4;

Het¹ represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

X represents O or S;

R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} and R^{5f} independently represent H or C_{1-3} alkyl;

R² and R³ independently represent H, C₁₋₄ alkyl (optionally substituted and/or terminated with one or more nitro or cyano groups), OR⁷, N(R^{7a})R^{7b}, OC(O)R⁸ or together form -O-(CH₂)₂-O-, -(CH₂)₃-, -(CH₂)₄- or
5 -(CH₂)₅-;

R⁷ and R⁸ independently represent H, C₁₋₆ alkyl or -(CH₂)_b-aryl (which latter two groups are optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, C₁₋₄ alkyl and/or C₁₋₄ alkoxy);

10 R^{7a} and R^{7b} independently represent H or C₁₋₆ alkyl;
b represents 0, 1, 2, 3 or 4;

R⁴ represents H or C₁₋₆ alkyl;

15 D represents H, C₁₋₄ alkyl, -OR⁹, or -(CH₂)_cN(R¹⁰)(R¹¹);

R⁹ represents H, C₁₋₆ alkyl, -C(O)R¹², -(CH₂)_d-aryl or -(CH₂)_d-Het² (which latter three groups are optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, C₁₋₄ alkyl, C₁₋₄ alkoxy, C(O)R¹³, C(O)OR¹⁴ and/or -N(H)S(O)_eR¹⁵);

20 R¹⁰ represents H, C₁₋₆ alkyl, -(CH₂)_f-aryl, -C(NH)NH₂, -S(O)₂R^{15a}, -[C(O)]_gN(R¹⁶)(R¹⁷), -C(O)R¹⁸ or -C(O)OR¹⁹;

e represents 0, 1 or 2;

g represent 1 or 2;

R¹¹ represents H, C₁₋₆ alkyl, -C(O)R²⁰ or -(CH₂)_h-aryl (which latter group
25 is optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl and/or C₁₋₆ alkoxy);

R¹², R¹³, R¹⁴, R¹⁶, R¹⁷, R¹⁸, R¹⁹ and R²⁰ independently represent H, C₁₋₆ alkyl, Het³ or -(CH₂)_j-aryl (which latter three groups are optionally

substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl and/or C₁₋₆ alkoxy);

R¹⁵ and R^{15a} independently represent C₁₋₆ alkyl, aryl or -(CH₂)_k-aryl (all of which are all optionally substituted and/or terminated (as appropriate) by one or more substituents chosen from halo, nitro, C₁₋₆ alkyl and/or C₁₋₆ alkoxy);

c, d, f, h, j and k independently represent 0, 1, 2, 3 or 4;

Het² and Het³ independently represent five to ten-membered heterocyclic rings containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

R⁶ represents one or more optional substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl (optionally terminated by N(H)C(O)OR^{20a}), C₁₋₆ alkoxy, -C(O)N(H)R²¹, -NHC(O)N(H)R²², -N(H)S(O)₂R²³ and/or -OS(O)₂R²⁴;

R²¹ and R²² independently represent H or C₁₋₆ alkyl;

R^{20a}, R²³ and R²⁴ independently represent C₁₋₆ alkyl;

A represents a single bond, C₁₋₆ alkylene, -N(R²⁵)(CH₂)_m-, -O(CH₂)_m- or -(CH₂)_mC(H)(OR²⁵)(CH₂)_n- (in which latter three groups, the -(CH₂)_m- group is attached to the bispidine nitrogen atom and which latter four groups are optionally substituted by one or more -OH groups);

B represents a single bond, C₁₋₄ alkylene, -(CH₂)_pN(R²⁶)-, -(CH₂)_pS(O)_q-, -(CH₂)_pO- (in which three latter groups, the -(CH₂)_p- group is attached to the carbon atom bearing D and R⁴), -C(O)N(R²⁶)- (in which latter group, the -C(O)- group is attached to the carbon atom bearing D and R⁴),

-N(R²⁶)C(O)O(CH₂)_p- or -N(R²⁶)(CH₂)_p- (in which latter two groups, the N(R²⁶) group is attached to the carbon atom bearing D and R⁴);

m, n and p independently represent 0, 1, 2, 3 or 4;

q represents 0, 1 or 2;

5 R²⁵ represents H, C₁₋₆ alkyl or C(O)R²⁷;

R²⁶ represents H or C₁₋₆ alkyl;

R²⁷ represents H, C₁₋₆ alkyl, Het⁴ or -(CH₂)_r-aryl (which latter two groups are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl and/or C₁₋₆ alkoxy);

Het⁴ represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

r represents 0, 1, 2, 3 or 4;

15

or a pharmaceutically acceptable derivative thereof;

provided that:

- (a) R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e} and R^{5f} do not all simultaneously represent H;
- 20 (b) R^{5a} and R^{5b} do not represent C₁₋₃ alkyl when R^{5c}, R^{5d}, R^{5e} and R^{5f} all represent H; and
- (c) when D represents -OH or -(CH₂)_cN(R¹⁰)R¹¹ in which c represents 0, then:-

- (i) A does not represent -N(R²⁵)(CH₂)_m-, -O(CH₂)_m- or
- 25 -(CH₂)_mC(H)(OR²⁵)(CH₂)_n- (in which n is 0); and/or
- (ii) p does not represent 0 when B represents -(CH₂)_pN(R²⁶)-, -(CH₂)_pS(O)_q- or -(CH₂)_pO-.

2. A compound as claimed in Claim 1, wherein R^1 represents optionally substituted $-(CH_2)_a$ -phenyl, in which a is 0, 1, 2 or 3, or optionally substituted, optionally unsaturated, linear, branched or cyclic, C_{1-8} alkyl (which latter group may also be interrupted by an oxygen atom).

5

9 3. A compound as claimed in Claim 1 ~~or Claim 2~~, wherein R^2 represents H.

9
10

Claim 1
4. A compound as claimed in ~~any one of the preceding claims~~, wherein R^3 represents H.

9

Claim 1
5. A compound as claimed in ~~any one of the preceding claims~~, wherein R^4 represents H or C_{1-3} alkyl.

15

Claim 1
6. A compound as claimed in ~~any one of the preceding claims~~, wherein R^{5a} and R^{5b} either both represent H or both represent methyl.

9

Claim 1
7. A compound as claimed in ~~any one of the preceding claims~~, wherein R^{5c} , R^{5d} , R^{5e} and R^{5f} independently represent H or C_{1-2} alkyl.

20

9
8. A compound as claimed in ~~any one of the preceding claims~~, wherein R^6 ^{is an optional} ~~represents one or more~~ substituents selected from C_{1-6} alkyl (which alkyl group is optionally terminated by a $N(H)C(O)OR^{20a}$ group (in which R^{20a} represents C_{1-5} alkyl)), cyano, nitro, amino, $C(O)N(H)R^{21}$ and/or
25 ~~$-N(H)S(O)_2R^{23}$~~ ^{or} wherein s is 1, 2, 3, 4, 5.

Claim 1
9. A compound as claimed in ~~any one of the preceding claims~~, wherein X represents O.

claim 1

- 9 10. A compound as claimed in ~~any one of the preceding claims~~, wherein A represents a single bond or linear, or branched, C_{1-4} alkylene (which group is also optionally interrupted by O).

claim 1

- 9⁵ 11. A compound as claimed in ~~any one of the preceding claims~~, wherein B represents a single bond, C_{1-4} alkylene, $-(CH_2)_pO-$ or $-(CH_2)_pN(R^{26})-$ (in which latter two cases p is 1, 2 or 3).

claim 1

9 10

12. A compound as claimed in ~~any one of the preceding claims~~, wherein D represents H, OR^9 (in which R^9 represents H, C_{1-3} alkyl or optionally substituted phenyl) or $N(H)R^{10}$ (in which R^{10} represents H or C_{1-4} alkyl).

- 15 13. A pharmaceutical formulation including a compound as defined in ~~any one of Claims 1 to 12~~ in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

14. A pharmaceutical formulation for use in the prophylaxis or the treatment of an arrhythmia, comprising a compound as defined in ~~any one of Claims 1 to 12~~.

9 20

- 9 15. A compound as defined in ~~any one of Claims 1 to 12~~ for use as a pharmaceutical.

9 25

16. A compound as defined in ~~any one of Claims 1 to 12~~ for use in the prophylaxis or the treatment of an arrhythmia.

9

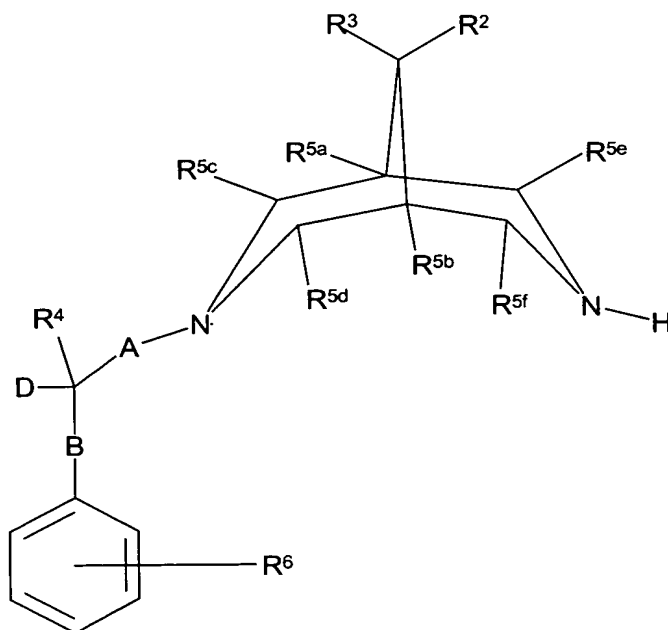
17. The use of a compound as defined in ~~any one of Claims 1 to 12~~ as active ingredient in the manufacture of a medicament for use in the prophylaxis or the treatment of an arrhythmia.

18. The use as claimed in Claim 17, wherein the arrhythmia is an atrial or a ventricular arrhythmia.

5 19. A method of prophylaxis or treatment of an arrhythmia which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 12 to a person suffering from, or susceptible to, such a condition.

10 20. A process for the preparation of a compound of formula I as defined in Claim 1 which comprises:

(a) reaction of a compound of formula II,



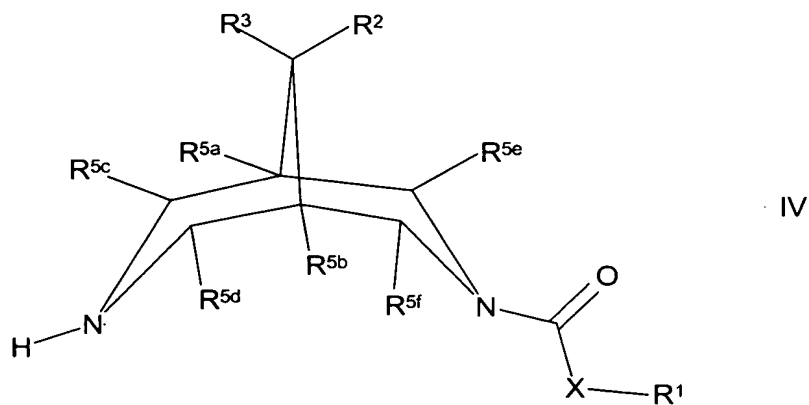
15 wherein R^2 , R^3 , R^4 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^6 , A, B and D are as defined in Claim 1 with a compound of formula III,



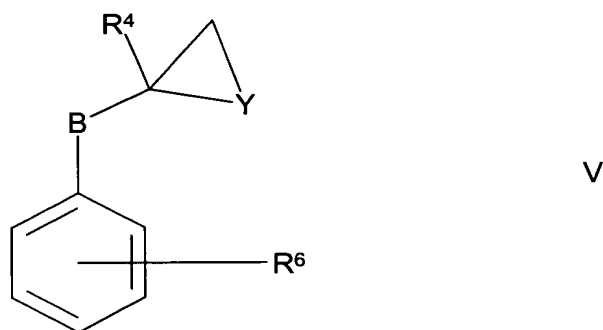
III

wherein L^1 represents a leaving group and R^1 and X are as defined in Claim 1;

(b) for compounds of formula I in which A represents CH_2 and D represents $-\text{OH}$ or $-\text{N(H)}\text{R}^{10}$, wherein R^{10} is as defined in Claim 1, reaction of a compound of formula IV,

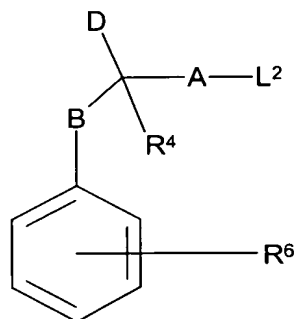


wherein R^1 , R^2 , R^3 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} and X are as defined in Claim 1, with a compound of formula V,



wherein Y represents O or $\text{N(R}^{10}\text{)}$ and R^4 , R^6 , R^{10} and B are as defined in Claim 1;

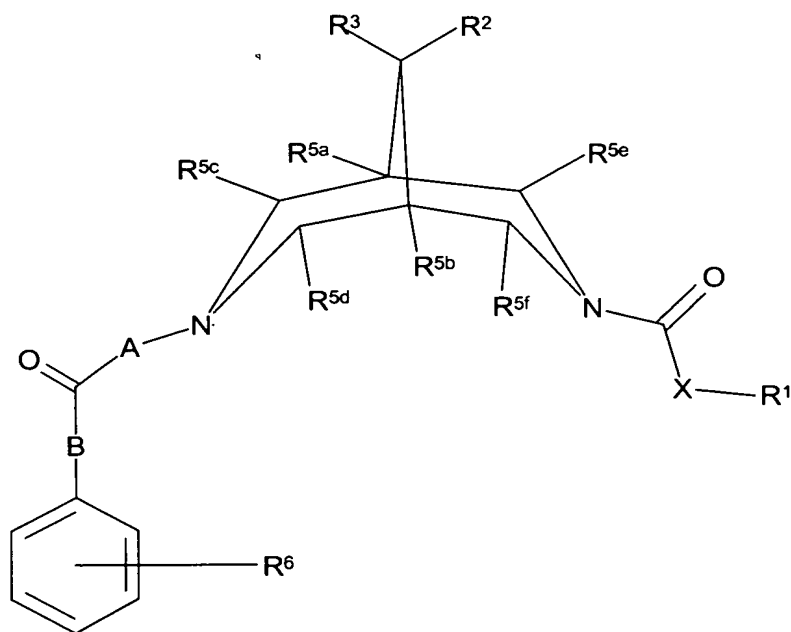
(c) reaction of a compound of formula IV, as defined above, with a compound of formula VI,



VI

wherein L^2 represents a leaving group and R^4 , R^6 , A, B and D are as defined in Claim 1;

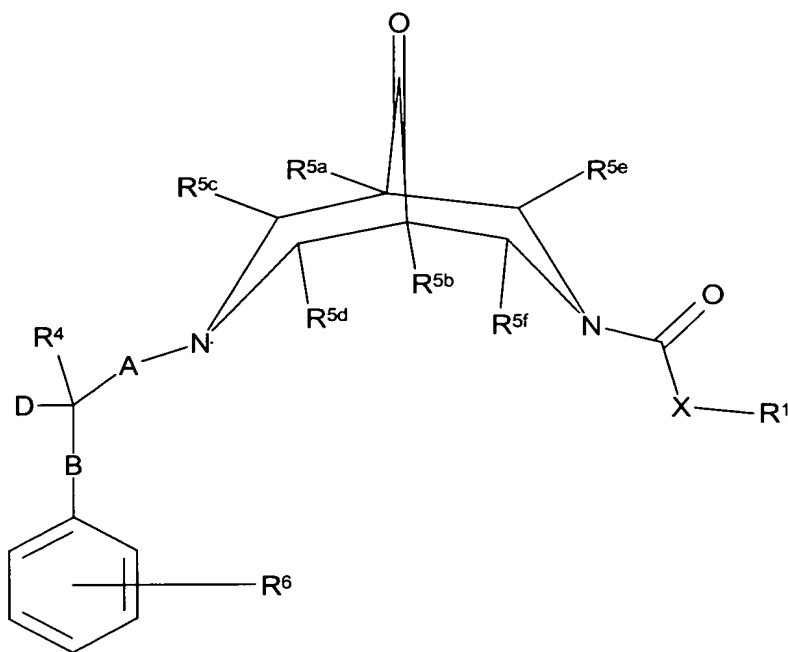
- 5 (d) for compounds of formula I in which D represents H or OH and R^4 represents H, reduction of a compound of formula VII,



VII

- 10 wherein R^1 , R^2 , R^3 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^6 , A, B and X are as defined in Claim 1;

(e) for compounds of formula I in which one of R^2 and R^3 represents H or OH and the other represents H, reduction of a corresponding compound of formula VIII,



VIII

wherein R^1 , R^4 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^6 , A, B, D and X are as
 5 defined in Claim 1;

(f) for compounds of formula I in which R^2 and/or R^3 represent $OC(O)R^8$ and R^8 is as defined in Claim 1, coupling of a corresponding compound of formula I in which R^2 and/or R^3 (as appropriate) represent OH and a compound of formula VIIIA,

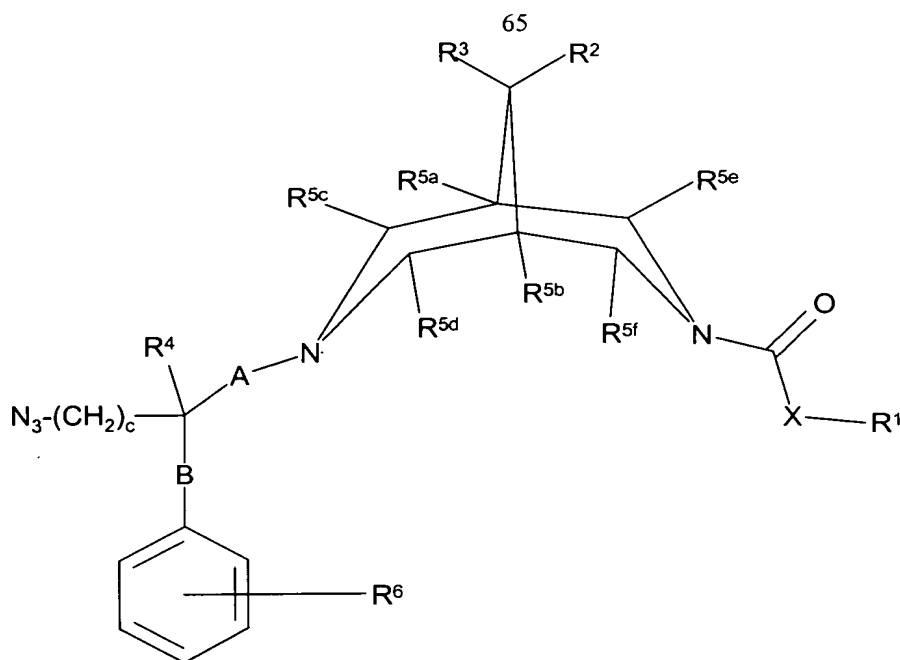
10



VIIIA

wherein R^8 is as defined in Claim 1;

(g) for compounds of formula I in which D represents $-(CH_2)_cNH_2$, reduction of a corresponding compound of formula IX,

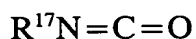


IX

wherein c , R^1 , R^2 , R^3 , R^4 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^6 , A , B and X are as defined in Claim 1;

- (h) for compounds of formula I in which D represents $-N(R^{11})C(O)NH(R^{17})$,
 5 in which R^{11} and R^{17} are as defined in Claim 1, except that R^{11} does not represent $C(O)R^{20}$, reaction of a corresponding compound of formula I in which D represents $-N(R^{11})H$, in which R^{11} is as defined in Claim 1 except that it does not represent $C(O)R^{20}$ in which R^{20} is as defined in Claim 1, with a compound of formula X,

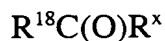
10



X

wherein R^{17} is as defined in Claim 1;

- (i) for compounds of formula I in which D represents $-N(H)[C(O)]_2NH_2$, reaction of a corresponding compound of formula I in which D represents $-NH_2$ with oxalic acid diamide;
- 15 (j) for compounds of formula I in which D represents $-N(R^{11})C(O)R^{18}$, in which R^{11} and R^{18} are as defined in Claim 1, except that R^{11} does not represent $C(O)R^{20}$, reaction of a corresponding compound of formula I in which D represents $-N(R^{11})H$, in which R^{11} is as defined in Claim 1 except that it does not represent $C(O)R^{20}$, with a compound of formula XI,



XI

wherein R^x represents a suitable leaving group and R^{18} is as defined in Claim 1;

- (k) for compounds of formula I in which D represents $-N(H)R^{10}$ and R^{10} is as defined in Claim 1 except that it does not represent H or $-C(NH)NH_2$,
 5 reaction of a corresponding compound of formula I wherein D represents $-NH_2$ with a compound of formula XIA,



XIA

- wherein R^{10a} represents R^{10} as defined in Claim 1, except that it does not
 10 represent H or $-C(NH)NH_2$ and L^1 is as defined above;

(l) for compounds of formula I which are bispidine-nitrogen N-oxide derivatives, oxidation of the corresponding bispidine nitrogen of a corresponding compound of formula I;

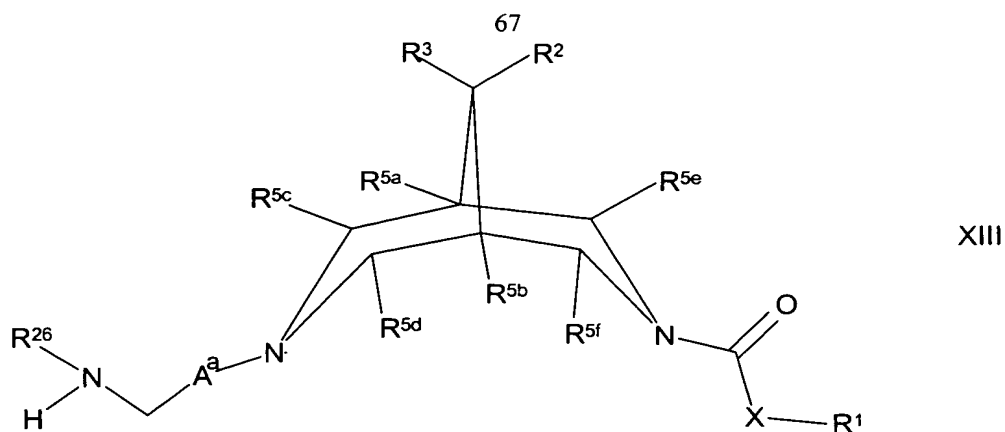
- (m) for compounds of formula I which are C_{1-4} alkyl quaternary ammonium
 15 salt derivatives, in which the alkyl group is attached to a bispidine nitrogen, reaction, at the bispidine nitrogen, of a corresponding compound of formula I with a compound of formula XII,



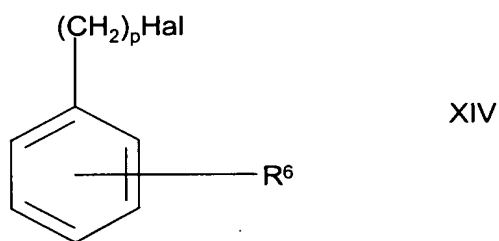
XII

wherein R^a represents C_{1-4} alkyl and Hal represents Cl, Br or I;

- (n) for compounds of formula I in which D and R^4 both represent H, A
 20 represents C_{1-6} alkylene, B represents $-N(R^{26})(CH_2)_p-$ and R^{26} and p are as defined in Claim 1, reaction of a compound of formula XIII,



wherein A^a represents C₁₋₆ alkylene and R¹, R², R³, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R²⁶ and X are as defined in Claim 1 with a compound of formula XIV,



wherein R⁶ and p are as defined in Claim 1 and Hal is defined above;

(o) reaction of a compound of formula II, as defined above, with a compound of formula XV,



wherein R¹ and X are as defined in Claim 1, in the presence of 1,1'-carbonyldiimidazole;

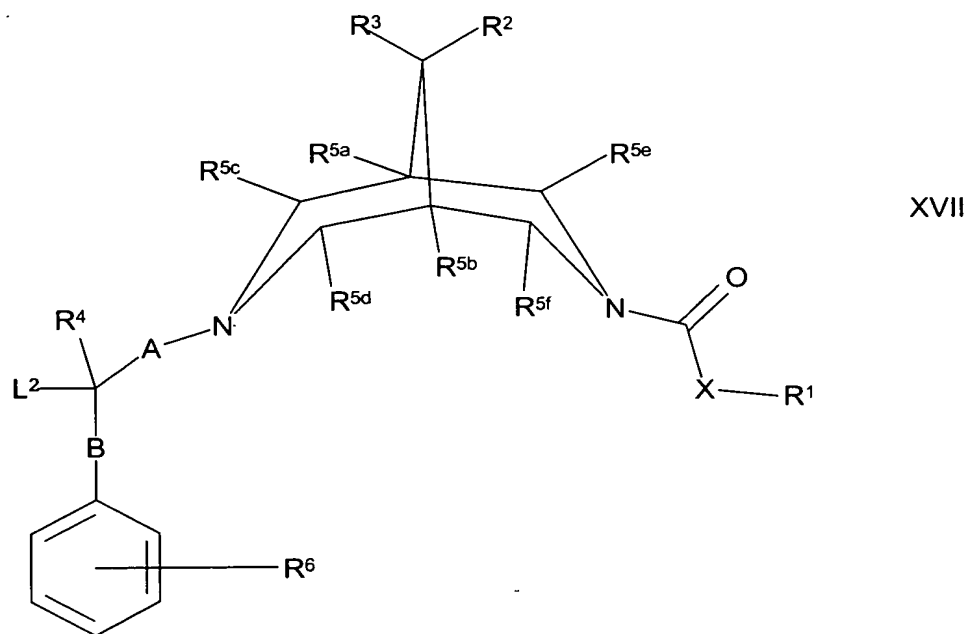
(p) for compounds of formula I in which R⁹ represents optionally substituted C₁₋₆ alkyl, optionally substituted -(CH₂)_d-aryl or optionally substituted

-(CH₂)_d-Het², reaction of a corresponding compound of formula I, in which D represents OH with a compound of formula XVI,



wherein R^{9a} represents optionally substituted C_{1-6} alkyl, optionally substituted $-(CH_2)_d$ -aryl or optionally substituted $-(CH_2)_d$ -Het², and d and Het² are as defined in Claim 1;

- (q) for compounds of formula I in which R^9 represents optionally substituted C_{1-6} alkyl, optionally substituted $-(CH_2)_d$ -aryl or optionally substituted $-(CH_2)_d$ -Het², reaction of a compound of formula XVII,



- wherein L^2 is as defined above and R^1 , R^2 , R^3 , R^4 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^6 , X, A and B are as defined in Claim 1 with a compound of formula XVI as defined above;

(r) for compounds of formula I in which R^9 represents $C(O)R^{12}$ and R^{12} is as defined in Claim 1, reaction of a corresponding compound of formula I in which D represents OH with a compound of formula XVIII,



wherein R^{12} is as defined in Claim 1;

(s) for compounds of formula I in which one or both of R^2 and R^3 represent $-N(R^{7a})R^{7b}$ in which one or both of R^{7a} and R^{7b} represents C_{1-6} alkyl, alkylation of a corresponding compound of formula I in which R^2

and/or R^3 represent $-N(R^{7a})R^{7b}$ (as appropriate) in which R^{7a} and/or R^{7b} (as appropriate) represent H, using a compound of formula XVIIIA,



XVIII A

wherein R^{7c} represents C_{1-6} alkyl and L^1 is as defined above;

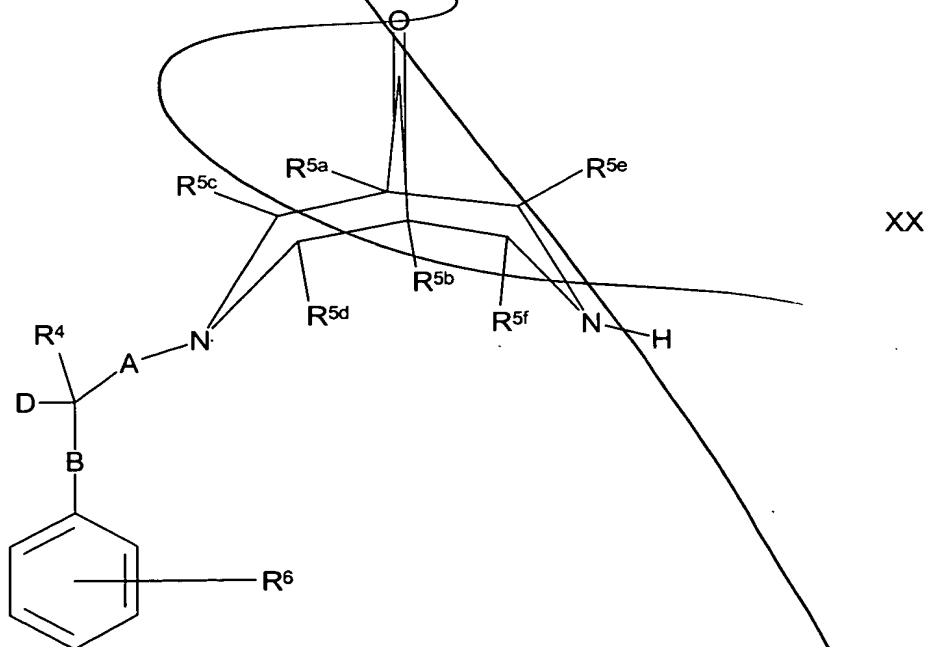
- 5 (t) conversion of one R^6 substituent to another; or
 (u) deprotection of a protected derivative of a compound of formula I as defined in Claim 1.

10 21. A compound of formula II as defined in Claim 20, or a protected derivative thereof.

22. A compound of formula IV as defined in Claim 20, or a protected derivative thereof.

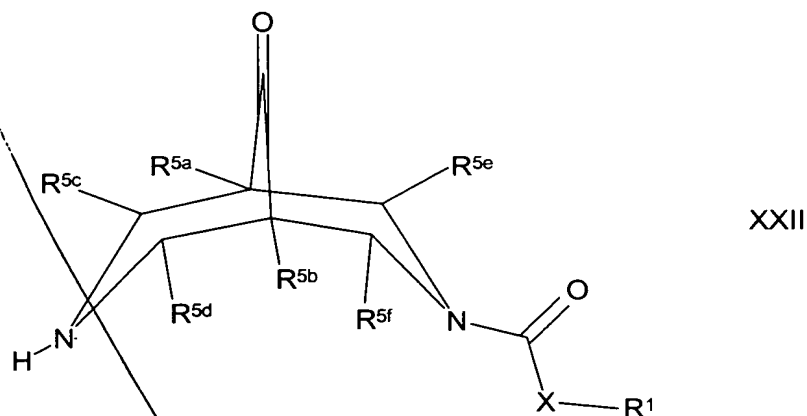
15 23. A compound of formula VIII as defined in Claim 20, or a protected derivative thereof.

24. A compound of formula XX,



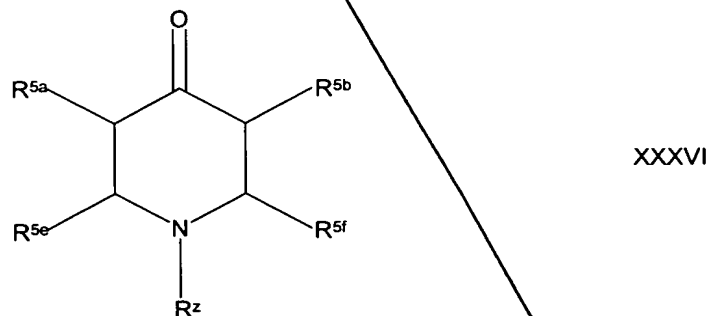
wherein R^4 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^6 , A, B and D are as defined in Claim 1, or a protected derivative thereof.

25. A compound of formula XXII,



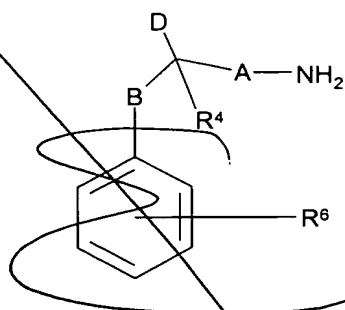
wherein R^1 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} and X are as defined in Claim 1, or a protected derivative thereof.

26. A process for the preparation of a compound of formula VIII, XX, XXII or XXXV (as defined herein, in which, in all cases, R^{5c} and R^{5d} both represent H), which comprises reaction of a compound of formula XXXVI,



wherein R^Z represents H or $-C(O)XR^1$ and R^1 , R^{5a} , R^{5b} , R^{5e} , R^{5f} and X are as defined in Claim 1, or a protected derivative thereof, with (as appropriate) either:

(1) a compound of formula XXXVII,



XXXVII

- or a protected derivative thereof, wherein R^4 , R^6 , A, B and D are as defined
- 5 in Claim 1; or
- (2) NH_3 (or a protected derivative thereof),
- in all cases in the presence of a formaldehyde.

add
B²